

Modulation of neurotransmitter release by carbon monoxide at the frog neuro-muscular junction

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Abstract

Carbon monoxide (CO) is an endogenous gaseous messenger, which regulates numerous physiological functions in a wide variety of tissues. Using extracellular microelectrode recording from frog neuro-muscular preparation the mechanisms of exogenous and endogenous CO action on evoked quantal acetyl-choline (Ach) release were studied. It was shown that CO application increases Ach-release in dose-dependent manner without changes in pre-synaptic Na⁺ and K⁺ currents. The effect of exogenous CO on Ach-release was decreased by prior application of guanylate cyclase inhibitor ODQ and prevented by application of a cyclic guanylate monophosphate (cGMP) analog 8Br-cGMP. Pre-treatment of the preparation with adenylate cyclase inhibitor MDL-12330A has completely abolished the effect of CO, whereas elevation of intracellular level of cyclic adenosine monophosphate (cAMP) mimicked and eliminated CO action. Application of cGMP-activated phosphodiesterase-2 inhibitor EHNA did not prevent CO action, whereas inhibition of cGMP-inhibited phosphodiesterase-3 by quazinone has partially blocked the effect of CO. Utilizing immuno-histochemical methods CO-producing enzyme heme-oxygenase-2 (HO-2) was shown to be expressed in skeletal muscle fibers, mostly in subsarcolemmal region, karyolemma and sarcoplasmic reticulum. Zn-protoporphirin-IX, the selective HO-2 blocker, has depressed Ach-release, suggesting the tonic activating effect of endogenous CO on pre-synaptic function. These results suggest that facilitatory effect of CO on Ach-release is mediated by elevation of intracellular cAMP level due to activation of adenylate cyclase and decrease of cAMP breakdown. As such, endogenous skeletal muscle-derived CO mediates tonic retrograde up-regulation of neuro-transmitter release at the frog neuro-muscular junction. © 2007 Bentham Science Publishers Ltd.

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Keywords

Acetyl-choline, cAMP, Carbon monoxide, Evoked acetyl-choline release, Heme-oxygenase 2, Neuro-muscular junction